

AMENDMENTS TO THE CLAIMS:**JC17 Rec'd PCT/PTO 20 SEP 2005**

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1-13. (cancelled)

14. (currently amended) A cholesterol-lowering therapy method, which method comprises the administration of melagatran ~~a low molecular weight thrombin inhibitor~~, or a pharmaceutically acceptable derivative thereof[[,]] to a patient in need of such therapy.

15. (cancelled)

16. (currently amended) The method ~~as claimed in~~ of Claim 14 ~~or Claim 15~~ wherein the therapy/treatment results in a decrease in serum levels of cholesterol, low-density lipoproteins, very low-density lipoproteins, triglycerides and/or apolipoprotein B; and/or an increase in serum levels of high-density lipoproteins and/or apolipoprotein A-I.

17. (cancelled)

18. (currently amended) The method ~~as claimed in~~ of Claim ~~14~~17, wherein the method comprises administering derivative of melagatran ~~is~~ a prodrug of melagatran.

19. (currently amended) The method ~~as claimed in~~ of Claim 18, wherein the method comprises delivering a prodrug ~~is~~ of the formula:

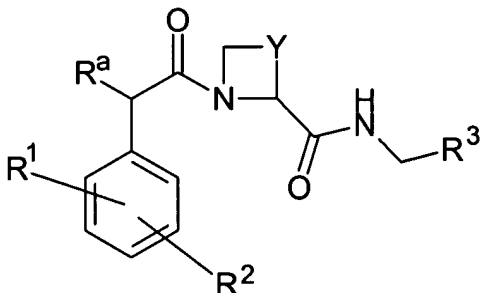


wherein R¹ represents linear or branched C₁₋₆ alkyl and the OH group replaces one of the amidino hydrogens in Pab.

20. (currently amended) The method ~~as claimed in~~ of Claim 19, wherein R¹ represents methyl, ethyl, or propyl.

21. (currently amended) The method ~~as claimed in~~ of Claim 20, wherein R¹ represents ethyl.

22. (currently amended) A cholesterol-lowering therapy method, which method comprises the administration of a thrombin inhibitor ~~The method as claimed in any one of Claims 14 to 16, wherein the thrombin inhibitor is of formula I,~~



wherein

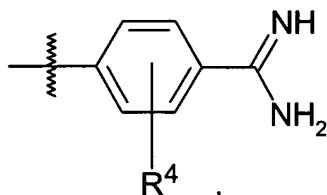
R^a represents -OH or -CH₂OH;

R¹ represents at least one optional halo substituent;

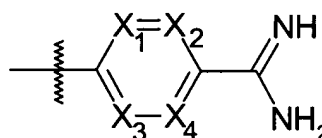
R² represents one or two C₁₋₃ alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;

Y represents -CH₂- or -(CH₂)₂-; and

R³ represents a structural fragment of formula I(i) or I(ii):



I(i)



I(ii)

wherein

R⁴ represents H or one or more fluoro substituents; and

one or two of X₁, X₂, X₃, and X₄ represent -N- and the others represent -CH-,

or a pharmaceutically acceptable derivative thereof, to a patient in need of such therapy.

23. (currently amended) The method ~~as claimed in~~ of Claim 22, wherein the thrombin inhibitor or derivative is:

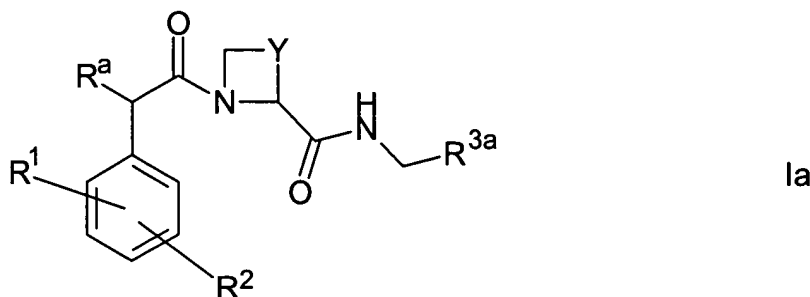
Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab;

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF); or

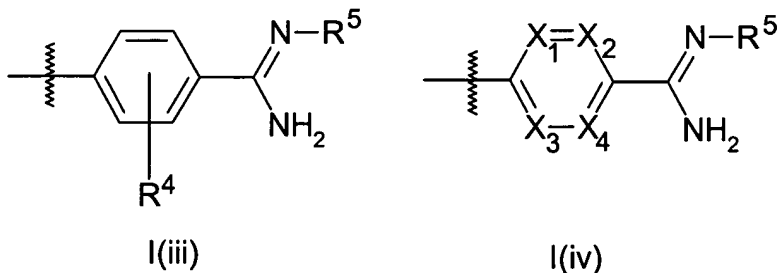
Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab.

24. (currently amended) The method ~~as claimed in~~ of Claim 22 or Claim 23, wherein the ~~derivative of the thrombin inhibitor or derivative~~ is a prodrug of a thrombin ~~that~~ inhibitor.

25. (currently amended) The method ~~as claimed in~~ of Claim 24, wherein the prodrug is of formula Ia,



wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



wherein R⁵ represents OR⁶ or C(O)OR⁷;

R⁶ represents H, C₁₋₁₀ alkyl, C₁₋₃ alkylaryl₁ or C₁₋₃ alkyloxyaryl₁ ~~[[()]]~~the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents~~[[()]]~~; and

R⁷ represents C₁₋₁₀ alkyl, ~~(which latter group is optionally interrupted by one or more oxygen atoms); or~~ C₁₋₃ alkylaryl₁ or C₁₋₃ alkyloxyaryl₁ ~~[[()]]~~the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected

from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents[[];]] and
~~R^a, R¹, R², Y, R⁴, X₁, X₂, X₃ and X₄ are as defined in Claim 22.~~

26. (currently amended) The method ~~as claimed in~~ of Claim 25, wherein the prodrug is:
 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe);
 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF)(OMe); or
 Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe).

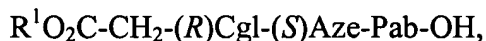
27. (original) A combination product comprising:
 (A) a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof; and
 (B) another cholesterol-lowering, or lipid-lowering/modifying, therapeutic agent,
 wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

28-29. (cancelled)

30. (currently amended) A ~~The combination product as claimed in any one of Claims Claim 27 to 29,~~ wherein the thrombin inhibitor or derivative is melagatran.

31. (currently amended) A ~~The combination product as claimed in of Claim 27~~ 30, wherein the thrombin inhibitor or derivative of melagatran is a prodrug of melagatran.

32. (currently amended) A ~~The combination product as claimed in of Claim 31,~~ wherein the prodrug is of the formula:

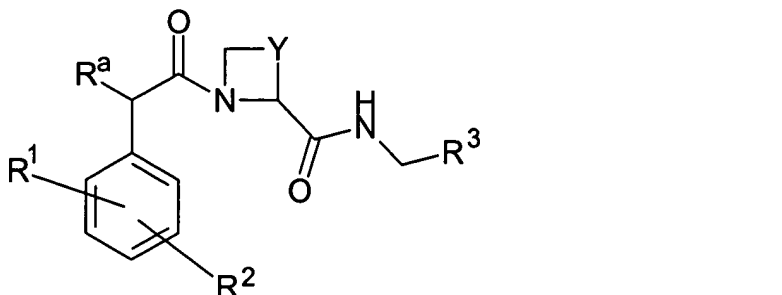


wherein R¹ represents linear or branched C₁₋₆ alkyl and the OH group replaces one of the amidino hydrogens in Pab.

33. (currently amended) A ~~The combination product as claimed in of Claim 32,~~ wherein R¹ represents methyl, ethyl, or propyl.

34. (currently amended) A ~~The combination product as claimed in~~ of Claim 33, wherein R¹ represents ethyl.

35. (currently amended) A ~~The combination product as claimed in any one of Claims Claim 27 to 29~~, wherein the thrombin inhibitor or derivative is a compound of formula I,



wherein

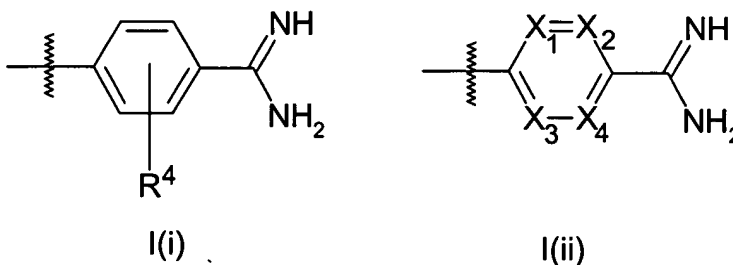
R^a represents -OH or -CH₂OH;

R¹ represents at least one optional halo substituent;

R² represents one or two C₁₋₃ alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;

Y represents -CH₂- or -(CH₂)₂-; and

R³ represents a structural fragment of formula I(i) or I(ii):



wherein

R⁴ represents H or one or more fluoro substituents; and

one or two of X₁, X₂, X₃, and X₄ represent -N- and the others represent -CH-.

36. (currently amended) A ~~The combination product as claimed in~~ of Claim 27 Claim 35, wherein the thrombin inhibitor or derivative is:

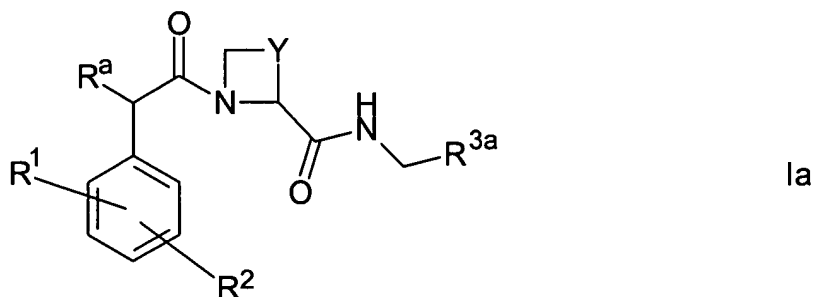
Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab;

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF); or

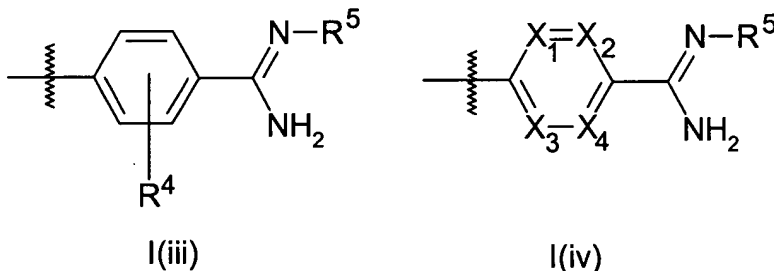
Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab.

37. (currently amended) A ~~The combination product as claimed in of Claim 27 Claim 35 or Claim 36~~, wherein the thrombin inhibitor or derivative of the thrombin inhibitor is a prodrug of a thrombin that inhibitor.

38. (currently amended) A ~~The combination product as claimed in of Claim 27 Claim 37~~, wherein the thrombin inhibitor or derivative is a prodrug is of formula Ia,



wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



wherein R⁵ represents OR⁶ or C(O)OR⁷;

R⁶ represents H, C₁₋₁₀ alkyl, C₁₋₃ alkylaryl or C₁₋₃ alkyloxyaryl, ~~[[()]]~~the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents~~[[()]]~~; and

R⁷ represents C₁₋₁₀ alkyl, ~~[[()]]~~which latter group is optionally interrupted by one or more oxygen atoms~~]; or~~ C₁₋₃ alkylaryl; or C₁₋₃ alkyloxyaryl, ~~[[()]]~~the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected

from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and
~~R^a, R¹, R², Y, R⁴, X₁, X₂, X₃ and X₄ are as defined in Claim 35.~~

39. (currently amended) A ~~The~~ combination product ~~as claimed in of Claim 27 38~~, wherein the thrombin inhibitor or derivative ~~prodrug~~ is:

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe);

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF)(OMe); or

Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe).

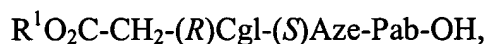
40. (currently amended) A ~~The~~ combination product ~~as claimed in any one of Claims Claim 27 to 39~~, wherein the other therapeutic agent is a statin.

41. (currently amended) A ~~The~~ combination product ~~as claimed in of Claim 27, 40~~ wherein the other therapeutic agent ~~statin~~ is lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, pitavastatin, or rosuvastatin.

42-44. (cancelled)

45. (new) The method of Claim 22, wherein the therapy/treatment results in a decrease in serum levels of cholesterol, low-density lipoproteins, very low-density lipoproteins, triglycerides and/or apolipoprotein B; and/or an increase in serum levels of high-density lipoproteins and/or apolipoprotein A-I.

46. (new) The combination product of Claim 27, wherein the thrombin inhibitor or derivative is of the formula:



wherein R¹ represents linear or branched C₁₋₆ alkyl and the OH group replaces one of the amidino hydrogens in Pab, and the other therapeutic agent is a statin.

47. (new) The combination product of Claim 27, wherein the thrombin inhibitor or derivative is of the formula:



wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group replaces one of the amidino hydrogens in Pab, and the other therapeutic agent is lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, pitavastatin, or rosuvastatin.

48. (new) The combination product of Claim 27, wherein the thrombin inhibitor or derivative is of the formula:



wherein Et represents ethyl and the OH group replaces one of the amidino hydrogens in Pab, and the other therapeutic agent is a statin

49. (new) The combination product of Claim 27, wherein the thrombin inhibitor or derivative is of the formula:



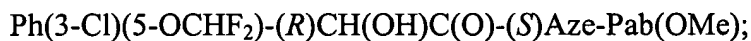
wherein Et represents ethyl and the OH group replaces one of the amidino hydrogens in Pab, and the other therapeutic agent is lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, pitavastatin, or rosuvastatin.

50. (new) The combination product of Claim 27, wherein the thrombin inhibitor or derivative is:



and the other therapeutic agent is a statin.

51. (new) The combination product of Claim 27, wherein the thrombin inhibitor or derivative is:



and the other therapeutic agent is a statin.

52. (new) The combination product of Claim 27, wherein the thrombin inhibitor or derivative is:

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab;

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF); or

Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab,

and the other therapeutic agent is lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, pitavastatin, or rosuvastatin.

53. (new) The combination product of Claim 27, wherein the thrombin inhibitor or derivative is:

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe);

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF)(OMe); or

Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe),

and the other therapeutic agent is lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, pitavastatin, or rosuvastatin.